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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MODIFIED MACROMOLECULES AND METHODS OF MAKING AND USING THEREOF

(57) Abstract: Described herein are compounds such as macromolecules that have been modified in order to facilitate crosslinking by introduction of at least one hydrazide-reactive group and/or aminoxy-reactive group, and methods of making and using thereof for scar-free wound healing, for delivering bioactive agents or living cells, for preventing adhesion after a surgical procedure or for bone and cartilage repair. The macromolecule can be an oligonucleotide, a nucleic acid, a polypeptide, a lipid, a glycoprotein, a glycolipid, a polysaccharide, a protein or a synthetic polymer, preferably a glycosaminoglycan like hyaluronan.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/040726

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C08B37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2004/037164 A (UNIVERSITY OF UTAH RESEARCH FOUNDATION; PRESTWICH, GLENN, D; SHU, XIAO) 6 May 2004 (2004-05-06) claims 1-107	1-223
X	US 5 874 417 A (PRESTWICH ET AL) 23 February 1999 (1999-02-23) claims 1-30 examples	1-223
X	US 6 630 457 B1 (AESCHLIMANN DANIEL ET AL) 7 October 2003 (2003-10-07) column 5, lines 31-65 column 13, lines 1-10 examples	1-223
A	US 5 880 270 A (BERNINGER ET AL) 9 March 1999 (1999-03-09) claims 1-36	1-223



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

8 March 2005

Date of mailing of the international search report

31/03/2005

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/040726

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004037164	A	06-05-2004	WO 2004037164 A2	06-05-2004
US 5874417	A	23-02-1999	US 5616568 A	01-04-1997
			AU 1260295 A	19-06-1995
			WO 9515168 A1	08-06-1995
			US 5652347 A	29-07-1997
US 6630457	B1	07-10-2003	AT 284229 T	15-12-2004
			AU 6192299 A	10-04-2000
			CA 2344215 A1	30-03-2000
			DE 69922522 D1	13-01-2005
			WO 0016818 A1	30-03-2000
			EP 1115433 A1	18-07-2001
			US 2004072793 A1	15-04-2004
US 5880270	A	09-03-1999	WO 9640662 A2	19-12-1996

PATENT COOPERATION TREATY

REC'D 29 MAR 2005

From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/040726

International filing date (day/month/year)
06.12.2004

Priority date (day/month/year)
04.12.2003

International Patent Classification (IPC) or both national classification and IPC
C08B37/00

Applicant
UNIVERSITY OF UTAH RESEARCH FOUNDATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/040726

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/040726

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-223
Inventive step (IS)	Yes: Claims	
	No: Claims	1-223
Industrial applicability (IA)	Yes: Claims	1-198
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item VIII

Certain observations on the international application

Although **claims 1, 14, 24, 25, 45, 46, 47, 48, 60, 61, 62, 63, 68, 69, 70, 71, 72, 73, 74, 82, 83, 84, 85, 99, 117, 118, 128, 147, 150, 151, 154, 155, 159, 166, 173, 185, 195, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 212, 213, 214, 215, 216, 217, 218, 219, 221 and 223** have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter.

The aforementioned claims therefore lack conciseness to a severe degree and as such do not meet the requirements of Article 6 PCT.

Reference is made to the following documents:

- D1:** WO 2004/037164 A (UNIVERSITY OF UTAH RESEARCH FOUNDATION; PRESTWICH, GLENN, D; SHU, XIAO) 6 May 2004
- D2:** US-A-5 874 417 (PRESTWICH ET AL) 23 February 1999
- D3:** US-B1-6 630 457 (AESCHLIMANN DANIEL ET AL) 7 October 2003
- D4:** US-A-5 880 270 (BERNINGER ET AL) 9 March 1999

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty

The subject-matter of **claims 1-223** is not novel over the documents D2 and D3 (Article 33(2) PCT).

D2 and D3 are directed to the modification of hyaluronic acid by way of functionalisation with an hydrazide, the crosslinking thereof and the formation of hydrogels, for use as tissue adhesive, tissue separator, drug delivery system, matrix for cell culture and temporary scaffold for tissue regeneration.

2. Inventive step

Since the subject-matter of **claims 1-223** is not novel, the question of inventive step appears to be superfluous (Article 33(3) PCT).

3. Industrial applicability

3.1. The subject-matter of present **claims 1-198** appears to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

3.2. For the assessment of the present **claims 199-223** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
D1	06.05.2004	15.05.2003	21.06.2002

This disclosure contains matter related to the subject-matter of **claims 1-223** although it does not constitute prior art within the meaning of rule 64.1(b) PCT. It could, however, be relevant for the assessment of novelty and inventive step, if the priority of the present application has not been validly claimed.